REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Ueno et al. (1988) in view of Drug Information Handbook, British Medical Journal (1970), Weinstein et al. (1997), and Kohl et al. (1991). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to employ a 12 mg dose of chlorpheniramine in a method of treating motion sickness since Ueno et al. (1988) teaches treatment of motion sickness with a 20 mg/kg dose in S. murinus, the Drug Information Handbook teaches that human dose of chlorpheniramine is 8-12 mg every 8-12 hours, the British medical journal teaches antihistamines are useful for treating vomiting, a symptom of motion sickness, Weinstein et al. (1997) teach common agents for treating symptoms of motion sickness are antihistamines, and Kohl et al. (1991) teach that an oral antihistamine terfenadine can be used to treat motion sickness. The Examiner suggests that one of skill would have been motivated to employ chlorpheniramine at a 12 mg dose to treat motion sickness, however, no specific logic is described for this statement by the Examiner. Applicants respectfully disagree with the Examiner's conclusions regarding these prior art references.

As discussed in previous replies during prosecution of this case (dated 11/21/2006 and 5/7/2007), Ueno et al. (1988) disclose use of several different drugs, including chlorpheniramine, to treat symptoms of motion sickness in an animal model for motion sickness. The chlorpheniramine was administered subcutaneously at a dose of 20 mg/kg. Nowhere does this reference teach use of any other dose or route of administration of chlorpheniramine, especially not a dose that is 2 orders of magnitude lower than 20 mg/kg. It should be noted that a 12 mg dose in a human, as is claimed in claim 1, is equivalent to a dose of about 0.2 mg/kg (12 mg divided by average human body weight of 70 kg). Most importantly, it is a well-established general principle of pharmacology, taught in basic textbooks (e.g., *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E. Limbird (eds.), McGraw Hill: New York) that a pharmacological effect of a drug, its efficacy, is defined by the principle of dose-response. In the case of a drug such as chlorpheniramine, a drug that produces its effects through activity on receptors (see chapter 25 of *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E. Limbird (eds.), McGraw Hill: New York), a dose-response relationship is defined routinely as an s-shaped curve (see page 39 of chapter 2 from *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E. Limbird (eds.), McGraw Hill: New York). With such a dose-response relationship, pharmacological activity, or drug efficacy, increases as dose increases, in a steady, almost linear manner at some doses.

However, at very low doses, there is often no detectable activity. As a result, it is not supported by general principles of pharmacology that one of skill would understand or expect that a dose of a drug that is 2-orders of magnitude lower than a tested dose would produce a pharmacological effect or have efficacy. Additionally, Applicants have provide detailed discussion in previous replies (dated May 7, 2007 and October 8, 2007) of how teaching of a dose given by an entirely different route of administration (subcutaneously by Ueno et al. versus orally as claimed) does not provide one of skill with en expectation of success of using a drug effectively by another route.

The Examiner suggests that the reference *Drug Information Handbook* teaches that a human dose of chlorpheniramine is 8-12 mg every 8-12 hours. However, as pointed out in the previous reply (dated August 8, 2007), there are several different statements under "usual dosage" of chlorpheniramine. For example, oral doses in children are stated to start at 0.35 mg/kg/day for chlorpheniramine and for adults given chlorpheniramine i.m., i.v., or s.c., the maximum dosage stated is 20 mg. These statements indicate that the route of administration affects dose just as the indication being treated. In the *Drug Information Handbook* the doses listed refer to the approved indication for chlorpheniramine which is NOT motion sickness treatment but treatment of symptoms of an allergic reaction (anti-histamine activity). In order to determine what an effective dosage would be for motion sickness,

one of skill in the art would need to see data on treatment of motion sickness.

The Examiner has then suggested that one of skill would turn to references on treatment of motion sickness that describe use of antihistamines for motion sickness or vomiting (British Medical Journal 1970; Weinstein et al. 1997; Kohl et al. 1991). However, if one carefully reviews each of these references it is seen that the dosages of the drugs discussed are much higher than 12 mg. British Medical Journal (1970) teaches that the antihistamines cyclizine, meclazine, and promethazine are useful for treating the symptom of vomiting at doses of 25 to 50 mg when tablets are given orally or 1 mg/ml when an elixir or syrup is taken orally (equivalent to from 60-70 mg based on human body weight). Nowhere does this reference mention chlorpheniramine nor any dose less than 25 mg orally. Weinstein et al. (1997) teaches use of over-the-counter antihistamines for motion sickness, specifically dimenhydrinate and cyclizine. The doses taught in this reference are 50 mg, doses much higher than 12 mg. Nowhere does this paper teach or suggest use of lower doses of any antihistamine to treat motion sickness. Additionally, careful of the second column of pate 392 of the paper reveals that even though many antihistamines have been tested for their ability to prevent motion sickness "a minority of these drugs have indicated adequate therapeutic utility…". Therefore, this paper is actually providing one of skill with a reason to doubt that data on antihistamines as a class will predict the activity of any particular antihistamine. Kohl et al. (1991) disclose that terfenadine, an antihistamine that does not cross the blood

brain barrier very effectively, at a dose of 300 mg orally can be used to control nausea induced by a rotating chair. No other dose of terfenadine is shown to be effective nor is there any teaching of a dose of chlorpheniramine. Each of the references that the Examiner relies on teaches either alone or when combined a dose of an entirely different antihistamine drug for treatment of motion sickness at a dose much larger than the dose claimed (12 mg). Moreover, without any data provided on the effect of chlorpheniramine to treat motion sickness at a dose level near the claimed dose (Ueno et al. teach a much higher dose of chlorpheniramine) it is not possible for one of skill to make or use the claimed invention at the much lower claimed dose. One of skill would lack an expectation of success as well as a motivation to try such a low dose. A listing of a dose of chlorpheniramine used to treat nasal allergic symptoms (the teaching of the *Drug Information Handbook*) fails to provide one of skill with either teaching or motivation to try that dose to treat an entirely different condition (motion sickness).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the cited prior art fails to teach the invention as claimed which is use of chlorpheniramine at a specific dose to decrease the signs and

symptoms of motion sickness. The art, when combined, teaches use of chlorpheniramine to treat symptoms of motion sickness only at much higher doses, 2 orders of magnitude higher doses, teaches chlorpheniramine to treat an allergic reaction, or teaches use of entirely different drugs to treat motion sickness but also at higher doses. One of skill would not expect that data on an entirely different drug at a much higher dose to suggest that chlorpheniramine given orally at 12 mg would be an effective drug to decrease the signs and symptoms of motion sickness. The Examiner's conclusions are without basis in the general principles and standards of pharmacology. Accordingly, the prior art references cited fail to establish a case of *prima facie* obviousness. Withdrawal of this rejection is respectfully requested.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **January 18, 2008**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515